

Function and mechanisms of gene movement in living cells

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ABSTRACT

Gene regulation is mediated by multiple, superimposed mechanisms. At the genetic level cis-regulatory sequences specify tissue- and developmental stage at which a gene is expressed by recruiting sequence-specific DNA binding proteins. Epigenetic mechanisms include the location of genes within the nucleus and recruitment of enzymatic activities that remodel chromatin and modify histones. We have limited understanding of how genes are targeted to nuclear sub-compartments, what machinery moves them or how location precisely affects gene expression. This is in part because methods to address these fundamental questions are limited to fixed cells. We will combine live cell imaging with gene targeting to develop experimental systems to probe molecular mechanisms of nuclear positioning and chromatin dynamics in the tissue-specific regulation of the immunoglobulin heavy chain gene locus. This locus is a physiologically highly relevant model system because it undergoes several forms of chromosomal movements that are essential for normal B cell development and immune function. These include repositioning from the nuclear periphery to the interior upon B cell differentiation, chromatin looping during recombination and association of a single allele with heterochromatin to enforce mono-allelic expression. The IgH locus also participates in oncogenic chromosomal translocations that involve inappropriate inter-chromosomal associations whose molecular basis remains unclear. The proposed experiments will thus lead to the development of a novel experimental system to probe fundamental aspects of gene regulation.

